WHAT IS CLAIMED IS:

1.   A method for obtaining a polynucleotide that has a modulatory effect on an immune response, or encodes a polypeptide that has a modulatory effect on an immune response, that is induced by a genetic vaccine vector, the method comprising:

creating a library of recombinant polynucleotides; and

screening the library to identify an optimized recombinant polynucleotide that has, or encodes a polypeptide that has, a modulatory effect on an immune response induced by a genetic vaccine vector;

wherein the optimized recombinant polynucleotide or the polypeptide encoded by the recombinant polynucleotide exhibits an enhanced ability to modulate an immune response compared to a non-recombinant polynucleotide from which the library was created.

2.   The method of claim 1, wherein the optimized recombinant polynucleotide is incorporated into a genetic vaccine vector.

3.   The method of claim 1, wherein the optimized recombinant polynucleotide, or a polypeptide encoded by the optimized recombinant polynucleotide, is administered in conjunction with a genetic vaccine vector.

4.   The method of claim 1, wherein the library of recombinant polynucleotides is created by a process selected from the group consisting of DNA shuffling, error-prone PCR, oligonucleotide-directed mutagenesis, uracil-mediated mutagenesis, and repair-deficient host mutagenesis.

5.   The method of claim 1, wherein the polynucleotide that has a modulatory effect on an immune response is obtained by:

(1) recombining at least first and second forms of a nucleic acid that is, or encodes a molecule that is, involved in modulating an immune response, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant polynucleotides; and

7   (2) screening the library to identify at least one optimized recombinant

8   polynucleotide that exhibits, either by itself or through the encoded molecule, an enhanced

9   ability to modulate an immune response than a form of the nucleic acid from which the

10   library was created.

1   6.   The method of claim 5, wherein the method further comprises the steps

2   of:

3   (3) recombining at least one optimized recombinant polynucleotide

4   with a further form of the nucleic acid, which is the same or different from the first and

5   second forms, to produce a further library of recombinant polynucleotides;

6   (4) screening the further library to identify at least one further

7   optimized recombinant polynucleotide that exhibits an enhanced ability to modulate an

8   immune response than a form of the nucleic acid from which the library was created.; and

9   (5) repeating (3) and (4), as necessary, until the further optimized

10   recombinant polynucleotide exhibits an further enhanced ability to modulate an immune

11   response than a form of the nucleic acid from which the library was created.

1   7.   The method of claim 1, wherein the optimized recombinant

2   polynucleotide encodes a peptide or polypeptide that can interact with a cellular receptor

3   involved in mediating an immune response, wherein the peptide or polypeptide acts as an

4   agonist or antagonist of the receptor.

1   8.   The method of claim 7, wherein the cellular receptor is a macrophage

2   scavenger receptor.

1   9.   The method of claim 7, wherein the cellular receptor is selected from

2   the group consisting of a cytokine receptor and a chemokine receptor.

1   10.   The method of claim 9, wherein the chemokine receptor is CCR6.

1   11.   The method of claim 7, wherein the peptide or polypeptide mimics the

2   activity of a natural ligand for the receptor but does not induce immune reactivity to the

3   natural ligand.

1   12.   The method of claim 7, wherein the library is screened by:

2   expressing the recombinant polynucleotides so that the encoded

3   peptides or polypeptides are produced as fusions with a protein displayed on the surface of a

4   replicable genetic package;

5   contacting the replicable genetic packages with a plurality of cells that

6   display the receptor; and

7   identifying cells that exhibit a modulation of an immune response

8   mediated by the receptor.

1   13.   The method of claim 12, wherein the replicable genetic package is

2   selected from the group consisting of a bacteriophage, a cell, a spore, and a virus.

1   14.   The method of claim 13, wherein the replicable genetic package is an

2   M13 bacteriophage and the protein is encoded by geneIII or geneVII.

1   15.   The method of claim 7, which method further comprises introducing the

2   optimized recombinant polynucleotide into a genetic vaccine vector and administering the

3   vector to a mammal, wherein the peptide or polypeptide is expressed and acts as an agonist

4   or antagonist of the receptor.

1   16.   The method of claim 7, which method further comprises producing the

2   peptide or polypeptide encoded by the optimized recombinant polynucleotide and

3   introducing the peptide or polypeptide into a mammal in conjunction with a genetic vaccine

4   vector.

1   17.   The method of claim 7, wherein the optimized recombinant

2   polynucleotide is inserted into an antigen-encoding nucleotide sequence of a genetic vaccine

3   vector.

1   18.   The method of claim 17, wherein the optimized recombinant

2 polypeptide is introduced into a nucleotide sequence that encodes an M-loop of an HBsAg

3 polypeptide.

1   19.   The method of claim 1, wherein the optimized recombinant

2 polynucleotide comprises a nucleotide sequence rich in unmethylated CpG.

1   20.   The method of claim 1, wherein the optimized recombinant

2 polynucleotide encodes a polypeptide that inhibits an allergic reaction.

1   21.   The method of claim 20, wherein the polypeptide is selected from the

2 group consisting of interferon-α, interferon-γ, IL-10, IL-12, an antagonist of IL-4, an

3 antagonist of IL-5, and an antagonist of IL-13.

1   22.   The method of 1, wherein the optimized recombinant polynucleotide

2 encodes an antagonist of IL-10.

1   23.   The method of claim 22, wherein the antagonist of IL-10 is soluble or

2 defective IL-10 receptor or IL-20/MDA-7.

1   24.   The method of claim 1, wherein the optimized recombinant

2 polynucleotide encodes a costimulator.

1   25.   The method of claim 24, wherein the costimulator is B7-1 (CD80) or

2 B7-2 (CD86) and the screening step involves selecting variants with altered activity through

3 CD28 or CTLA-4.

1   26.   The method of claim 24, wherein the costimulator is CD1, CD40,

2 CD154 (ligand for CD40) or CD150 (SLAM).

1   27.   The method of claim 24, wherein the costimulator is a cytokine.

1   28.   The method of claim 27, wherein the cytokine is selected from the

2   group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12,

3   IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, GM-CSF, G-CSF, TNF-α, IFN-α, IFN-γ, and IL-

4   20 (MDA-7).

1   29.   The method of 28, wherein the library of recombinant polynucleotides

2   is screened by testing the ability of cytokines encoded by the recombinant polynucleotides to

3   activate cells which contain a receptor for the cytokine.

1   30.   The method of claim 29, wherein the cells contain a heterologous

2   nucleic acid that encodes the receptor for the cytokine.

1   31.   The method of 28, wherein the cytokine is interleukin-12 and the

2   screening is performed by:

3   growing mammalian cells which contain the genetic vaccine vector in a

4   culture medium; and

5   detecting whether T cell proliferation or T cell differentiation is induced

6   by contact with the culture medium.

1   32.   The method of 28, wherein the cytokine is interferon-α and the

2   screening is performed by:

3   expressing the recombinant polynucleotides so that the encoded

4   peptides or polypeptides are produced as fusions with a protein displayed on the surface of a

5   replicable genetic package;

6   contacting the replicable genetic packages with a plurality of B cells;

7   and

8   identifying phage library members that are capable of inhibiting

9   proliferation of the B cells.

1   33.   The method of claim 28, wherein the immune response of interest is

2   differentiation of T cells to T_H1 cells and the screening is performed by contacting a

3   population of T cells with the cytokines encoded by the members of the library of

4   recombinant polynucleotides and identifying library members that encode a cytokine that

5   induces the T cells to produce IL-2 and interferon-γ.

1   34.   The method of claim 27, wherein the cytokine encoded by the optimized

2   recombinant polynucleotide exhibits reduced immunogenicity compared to a cytokine

3   encoded by a non-optimized polynucleotide, and the reduced immunogenicity is detected by

4   introducing a cytokine encoded by the recombinant polynucleotide into a mammal and

5   determining whether an immune response is induced against the cytokine.

1   35.   The method of claim 24, wherein the costimulator is B7-1 (CD80) or

2   B7-2 (CD86) and the cell is tested for ability to costimulate an immune response.

1   36.   The method of claim 1, wherein the optimized recombinant

2   polynucleotide encodes a cytokine antagonist.

1   37.   The method of claim 36, wherein the cytokine antagonist is selected

2   from the group consisting of a soluble cytokine receptor and a transmembrane cytokine

3   receptor having a defective signal sequence.

1   38.   The method of claim 36, wherein the cytokine antagonist is selected

2   from the group consisting of ΔIL-10R and ΔIL-4R.

1   39.   The method of claim 1, wherein the optimized recombinant

2   polynucleotide encodes a polypeptide capable of inducing a predominantly T_H1 immune

3   response.

1   40.   The method of claim 1, wherein the optimized recombinant

2   polynucleotide encodes a polypeptide capable of inducing a predominantly T_H2 immune

3   response.

1   41.   A method for obtaining a polynucleotide that encodes an accessory

2   molecule that improves the transport or presentation of antigens by a cell, the method

3   comprising:

4   creating a library of recombinant polynucleotides by subjecting to

5   recombination nucleic acids that encode all or part of the accessory molecule; and

6   screening the library to identify an optimized recombinant

7   polynucleotide that encodes a recombinant accessory molecule that confers upon a cell an

8   increased or decreased ability to transport or present an antigen on a surface of the cell

9   compared to an accessory molecule encoded by the non-recombinant nucleic acids.

1   42.   The method of claim 41, wherein the screening involves:

2   introducing the library of recombinant polynucleotides into a genetic

3   vaccine vector that encodes an antigen to form a library of vectors;

4   introducing the library of vectors into mammalian cells; and

5   identifying mammalian cells that exhibit increased or decreased

6   immunogenicity to the antigen.

1   43.   The method of claim 41, wherein the accessory molecule comprises a

2   proteasome or a TAP polypeptide.

1   44.   The method of claim 41, wherein the accessory molecule comprises a

2   cytotoxic T-cell inducing sequence.

1   45.   The method of claim 44, wherein the cytotoxic T-cell inducing

2   sequence is obtained from a hepatitis B surface antigen.

1   46.   The method of claim 41, wherein the accessory molecule comprises an

2   immunogenic agonist sequence.